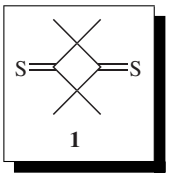
2,2,4,4-Tetramethylcyclobutane-1,3-dithione

Heimgartner, Heinz ; Mlostoń, Grzegorz

2,2,4,4-Tetramethylcyclobutane-1,3-dithione



1

[10181-56-3] $C_8H_{12}S_2$ (MW 172.32)

(reagent used as a stable thioketone; useful as a building block to introduce a cyclobutane moiety as a spacer unit)

Alternate Name: 2,2,4,4-tetramethyl-1,3-cyclobutanedithione.

Physical Data: mp 123–125 °C.

Solubility: soluble in hydrocarbons, chlorinated hydrocarbons, ethers, alcohols, pyridine, and other commonly used organic solvents; insoluble in water.

Form Supplied in: orange-red crystals, commercially not available.

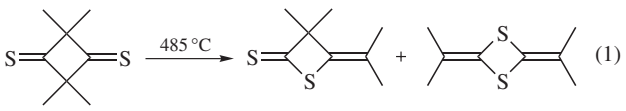
Analysis of Reagent Purity: single crystal X-ray analysis.[1]

Preparative Methods: the title reagent can be prepared by thionation of 2,2,4,4-tetramethylcyclobutane-1,3-dione with P_4S_{10} in pyridine at 110 °C[2–4] or with H_2S/HCl in methanol at −5 °C in the presence of $ZnCl_2$.[5]

Purification: column chromatography (silica gel, hexane/dichloromethane); less polar than 2,2,4,4-tetramethyl-3-thioxocyclobutanone; sublimation; recrystallization from cold methanol.

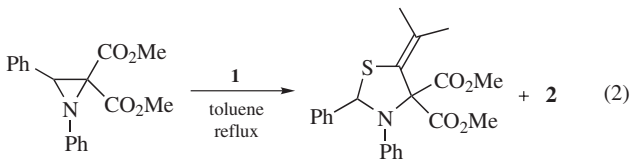
Handling, Storage, and Precautions: store in a refrigerator, safe in handling, camphoraceous odor.

Thermolysis. Pyrolysis of 2,2,4,4-tetramethylcyclobutane-1,3-dithione (**1**) at 485 °C in a quartz tube leads to a mixture of two new isomeric compounds **2** and **3** (eq 1).[1] Formally, both products are dimers of dimethyl thioketene, which is believed to be an intermediate.



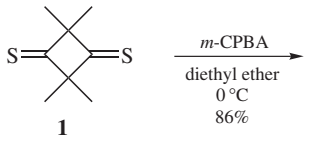
1 **2**, 80% **3**, 12% (1)

The formation of dimethyl thioketene from **1** is evidenced by the thermolysis carried out in the gas phase at 940 °C using FVP technique.[6] The reactive dimethyl thioketene can be trapped by dimethyl amine. In boiling toluene, **1** is partially dissociated and a [2 + 3]-cycloaddition of dimethyl thioketene with the azomethine ylide generated from aziridine **4** leads to **5** in 26% yield (eq 2).[7]

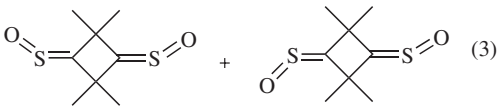


4 **5** + **2** (2)

Oxidation Reactions. Reaction of **1** with *m*-CPBA in diethyl ether at 0 °C affords a colorless solid consisting of *anti*- and *syn*-bis(sulfines) (**6a** and **6b**) (eq 3).[8] The ratio of the isomers depends on the reaction conditions. In tetrachloromethane at 70–75 °C, isomerization to the *anti*-isomer is achieved.

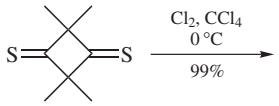


1

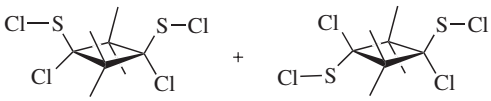


6a **6b** (3)

The chlorination of **1** with gaseous chlorine in tetrachloromethane at 0 °C leads to a mixture of *cis*- and *trans*-bis(α-chlorosulfanylchlorides) (**7a** and **7b**), respectively (eq 4).[9] Treatment of the mixture with thioacetic acid yields the corresponding acetylated disulfanes.[9]

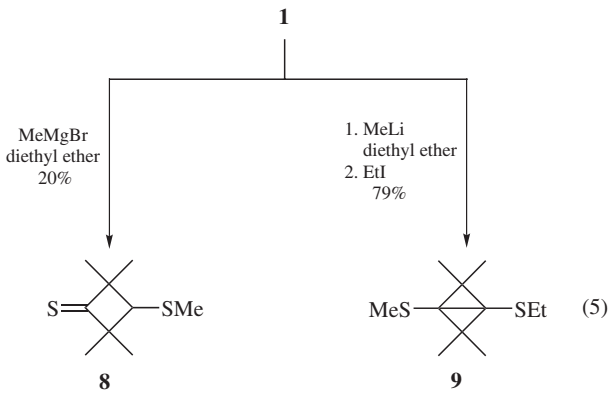


1



7a **7b** (4)

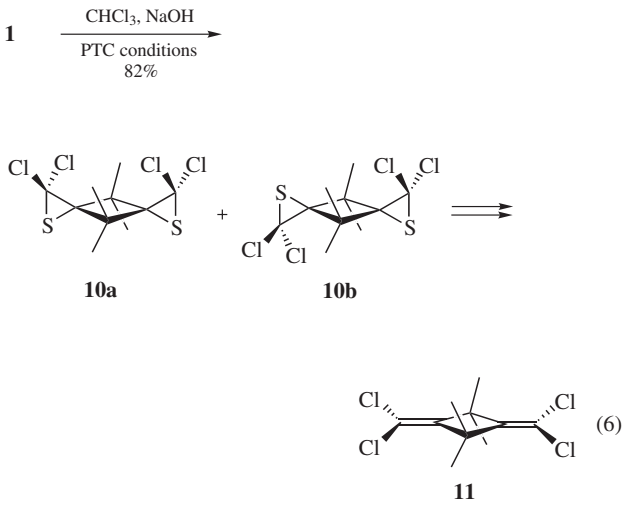
Reactions with Organometallics. The reaction of **1** with methylmagnesium iodide in ether gives **8** as the product of thiophilic addition.[10] However, the analogous reaction with methyllithium and subsequent alkylation yields 1,3-bis(alkylthio)bicyclo[1.1.0]butanes (**9**) (eq 5).[10]



8 **9** (5)

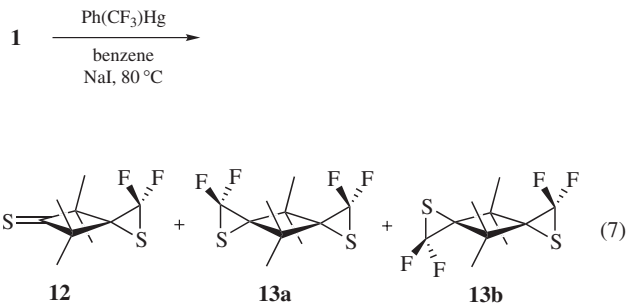
Reactions with Carbenes and Carbenoids. Under PTC conditions ($CHCl_3$, NaOH, TEBA), **1** is converted into a mixture of *cis*- and *trans*-bis(thiiranes) (**10a** and **10b**) in favor of the *cis*-isomer.[11] After prolonged reaction times, a stepwise desulfur-

ization takes place leading to 1,3-bis(dichloromethylene)cyclobutane derivative **11** (eq 6).



(6)

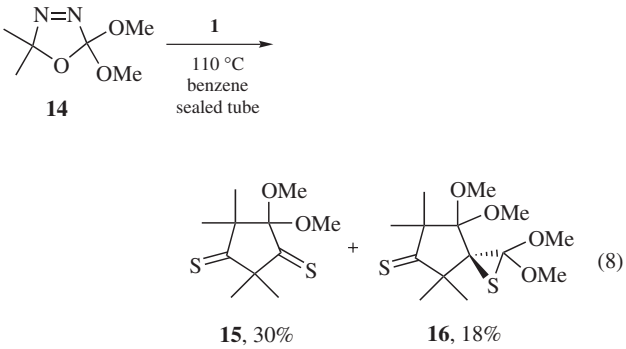
Heating of **1** and 1.1 equiv of (phenyl)(trifluoromethyl)mercury in benzene in the presence of sodium iodide affords, after 48 h, a mixture of three products, i.e., **12**, **13a**, and **13b** (eq 7).[12] By analogy to the reaction presented in eq 6, the ratio of **13a/13b** was ca. 4:1.



(7)

Difluorocarbene generated from bis(trifluoromethyl)cadmium in trichloromethane at −30 °C to rt adds to **1** to give, along with **12**, **13a**, and **13b** (total yield 50%), an unexpected 2,2-difluoro-1,3-dithiolane (so-called Schönberg product), which is the product of the interception of an intermediate thiocarbonyl difluoromethylide by **1**.[13]

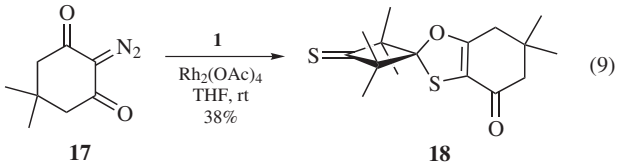
Dimethoxycarbene, generated by thermolysis of 2,5-dihydro-1,3,4-oxadiazole derivative **14**, reacts with **1** to give ring-enlarged products **15** and **16** (eq 8).[14] No dimethoxythiirane derivative of **1** can be detected in the reaction mixture.



(8)

The rhodium-catalyzed decomposition of diazo compound **17** in the presence of equimolar amounts of **1** leads to **18**, which is

the product of 1,5-dipolar electrocyclization of an intermediate α-keto-functionalized thiocarbonyl ylide (eq 9).[15]

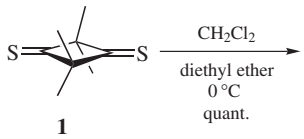


17 **18** (9)

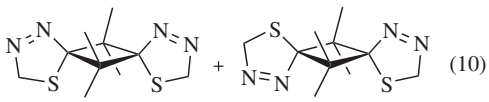
Reaction with 1,3-Dipoles

Diazo Compounds

Diazomethane adds easily to **1** in diethyl ether at 0 °C, and a mixture of *cis*- and *trans*-configured bis-adducts **19a** and **19b** is obtained as a colorless solid (eq 10).[4] Both cycloadditions occur regioselectively to give 1,3,4-thiadiazole derivatives. These compounds are relatively stable at rt but extrude nitrogen in refluxing chloroform when converted quantitatively into a stereoisomeric mixture of the corresponding dithiiranes.

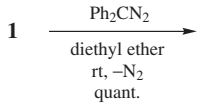


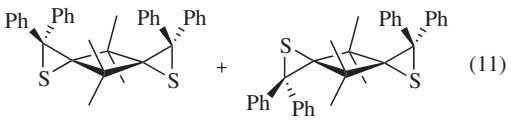
1



19a 3:7 **19b** (10)

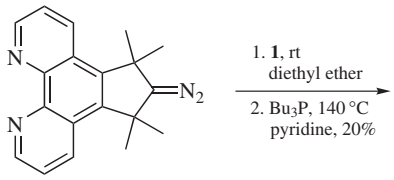
In the reaction of **1** with diphenyl diazomethane, the orange-red color of **1** disappears and immediate evolution of nitrogen is observed.[4] The product is a mixture of *cis*- and *trans*-dithiiranes (**20a** and **20b**) (eq 11). The reaction of **1** with 1 equiv of diphenyl diazomethane leading to the monothiirane is also described.[16]





20a 7:3 **20b** (11)

Reactions of different diazo compounds with **1** are carried out in order to prepare molecules that are used as rigid rod-like ligands,[17] with cyclobutane as a ferromagnetic coupling unit,[18,19] and as reversible redox systems.[20,21] In all procedures, the two-fold extrusion strategy[22] is applied. While the evolution of nitrogen occurs spontaneously, removal of sulfur is achieved by using phosphanes or phosphites. A representative example is outlined in eq 12.[17]



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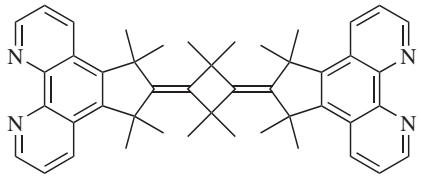
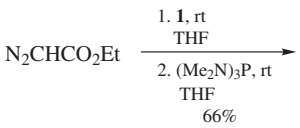


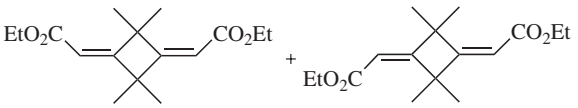
(12)

22

A limitation of the two-fold extrusion strategy appears when di(*tert*-butyl)diazomethane is used; treatment with 0.5 equiv of **1** in diethyl ether at −78 °C gives the expected 2:1 cycloadduct as a single isomer in 68% yield.[23] However, the thermal elimination of nitrogen as well as the attempted desulfurization with triphenylphosphane at variable temperatures do not lead to the expected sterical, highly congested alkenes.

Less reactive diazo compounds such as α-diazo esters, amides, and ketones react slowly with **1** and, therefore, these conversions must be catalyzed by the addition of $LiClO_4$. The reaction of **1** with ethyl diazoacetate affords mixtures of stereoisomeric bis(thiiranes) which, by desulfurization with tris(dimethylamino) phosphane, are converted into isomeric dicarboxylates (**23a** and **23b**) in equal amounts[24] (eq 13).

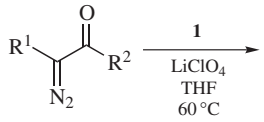




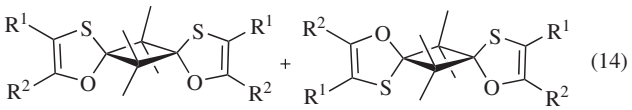
(13)

23a **23b**

On the other hand, the products obtained from the reaction of **1** with α-diazo ketones (**24**) are *cis*- and *trans*-bis(1,3-oxathiols) of type **25** (eq 14).[15,25] The formation of these products results from double 1,5-dipolar electrocyclization of the intermediate α-keto functionalized thiocarbonyl ylide. Obviously, the alternative 1,3-dipolar electrocyclizations leading to thiiranes are not able to compete.



24

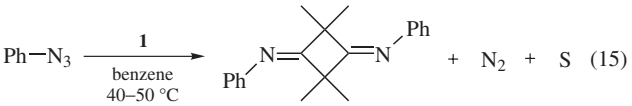


(14)

25a **25b**

Organic Azides

Heating of **1** in excess phenylazide at 40–50 °C leads to bis(*N*-phenylimine) (**26**) after spontaneous extrusions of nitrogen and sulfur (eq 15).[26] Unstable derivatives of 1,2,3,4-thiatriazole and thiaziridine are believed to be intermediates.

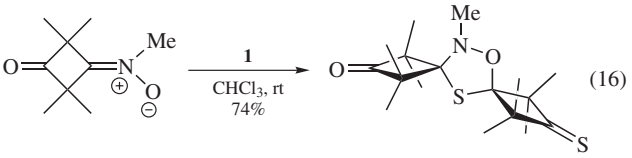


(15)

26, 70%

Nitrones

Cyclic and non-cyclic nitrones react easily with **1** at rt, but in solution the [2+3]-cycloadducts exist in equilibrium with the starting materials. Reactions carried out with 2 equiv of cyclic nitrones lead to 2:1 adducts which are, most likely, mixtures of *cis*/*trans*-isomers.[3] Reaction of nitrone **27** and **1** in trichloromethane at rt gives the orange-red 1,4,2-oxathiazolidine (**28**) in 74% yield (eq 16).[27] An analogous product was obtained in 84% yield with *N*-methyl benzophenonimine *N*-oxide.[28]

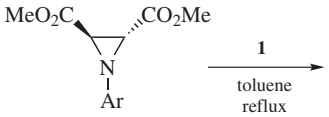


(16)

27 **28**

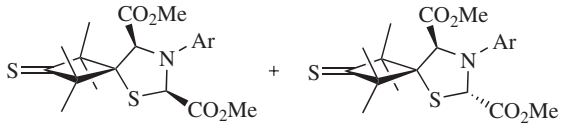
Azomethine Ylides

trans-*N*-(4-Methoxyphenyl)aziridine-2,3-dicarboxylate (**29**) reacts with **1** in boiling toluene to give a mixture of two diastereoisomeric 1:1 adducts **30a** and **30b** (eq 17). Formation of the *cis*-isomer (**30a**) results from the expected reaction course via conrotatory ring opening of **29** to give the (*E*,*E*)-configured azomethine ylide, which undergoes a stereoselective [2+3]-cycloaddition with **1**.[7] Partial isomerization of the azomethine ylide to the (*E*,*Z*)-configured isomer is responsible for the formation of **30b** as a minor product. No 2:1 adduct is formed.



29

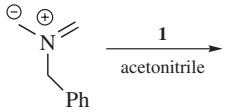
Ar = 4-MeOC$_6$H$_4$



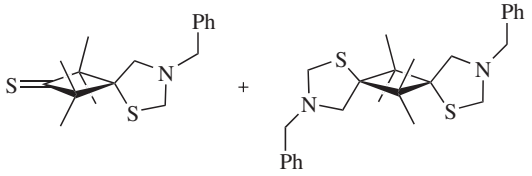
(17)

30a, 48% **30b**, 11%

The *N*-benzyl substituted azomethine ylide **31**, generated by using a desilylation method supported by ultrasound, adds to **1** in acetonitrile to give predominantly the 1:1 adduct **32**. Using a two-fold excess of the precursor of **31**, the *trans*-configured 2:1 adduct **33** is formed in low yield as the only stereoisomer (eq 18).[29]



31

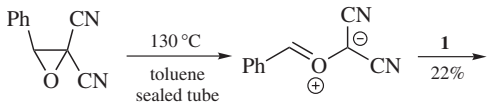


(18)

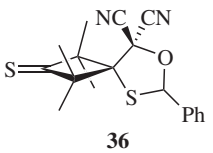
32, 65% **33**, 11%

Carbonyl Ylides

Heating a solution of equimolar amounts of **1** and 3-phenyloxirane-2,2-dicarbonitrile (**34**) in toluene gives 1,3-oxathiolane (**36**) in 22% yield (eq 19).[30] The formation of **36** results from the regioselective [2+3]-cycloaddition of the thermally generated carbonyl ylide with **1**.



34 **35**



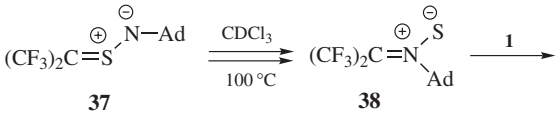
(19)

36

Thiocarbonyl S-imides

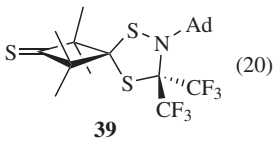
Hexafluorothioacetone *S*-imide (**37**) reacts with **1** only at elevated temperatures. The product formed is 1,4,2-dithiazolidine (**39**), which is an isomer of the expected [2+3]-cycloadduct.[31] Therefore, the reaction pathway is explained by the isomerization

of **37** to the putative thionitrone **38**, which undergoes a [2+3]-cycloaddition with **1** to yield **39** (eq 20).



37 **38**

Ad = Adamantan-1-yl

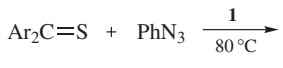


(20)

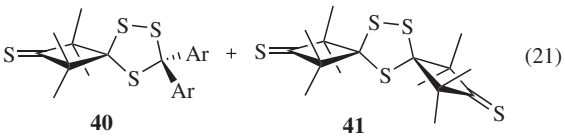
39

Thiocarbonyl S-sulfides (Thiosulfines)

The products obtained from three-component reactions of an aromatic thioketone, phenyl azide, and **1** are 1,2,4-trithiolanes (**40** and **41**), formed along with *N*-phenyl diarylimines (eq 21).[32] The trithiolanes are interception products of the corresponding thiocarbonyl *S*-sulfide, which is generated in situ by sulfur-transfer from an intermediate thiaziridine to **1**, with either the aromatic thioketone or another molecule of **1**. No products of secondary cycloadditions are formed.



Ar = 4-MeOC$_6$H$_4$

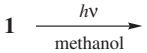


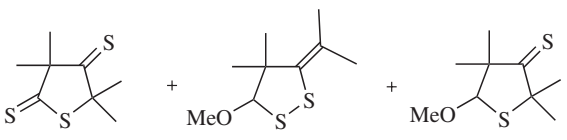
(21)

40 **41**

A similar reaction with methyl dithiobenzoate instead of the aromatic thioketone, in which **41** is formed in low yield along with a 1,4,2-dithiazolidine obtained from an intermediate thiocarbonyl *S*-imide and **1**, is also reported.[33]

Ring-Enlargement Reactions. A ring enlargement of **1** via insertion of dimethoxycarbene is presented in eq 8.[14] Photolysis of **1** in methanolic solution yields five-membered sulfur heterocycles (**42**–**44**) (eq 22).[34] A similar mixture of products is obtained, in addition to **1**, when dithiolactone **2**, which is an isomer of **1**, is irradiated with UV-light in methanol or cyclohexane.[35,36]





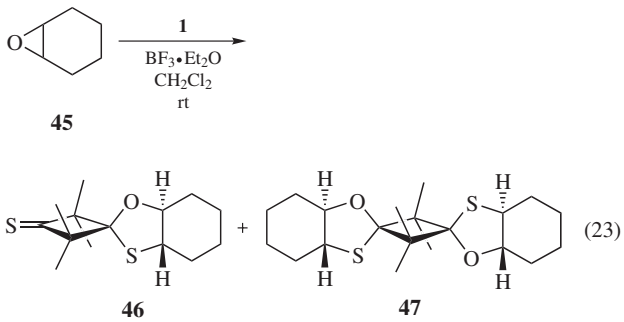
(22)

42 **43** **44**

3-Thioxodithiolactone (**42**) is formed in 55% yield when a solution of **1** in acetone is treated with elemental sulfur in the presence of sodium thiophenolate.[37]

Base-Catalyzed Isomerization. The isomerization of **1** into dithiolactone **2** is easily achieved in boiling benzene with catalytic amounts of sodium methanolate.[1,36] Other basic agents can also be used.[1] The electrochemically induced isomerization of **1** into **2** is also reported.[38]

Miscellaneous. The reaction of **1** with cyclohexene oxide (**45**) in dichloromethane catalyzed by borontrifluoride occurs at rt and leads to a complex mixture of mono- and diastereoisomeric bis-adducts (eq 23).[39] Along with the expected 1,3-oxathiolanes (**46** and **47**), secondary products containing a 1,3-dithiolane ring or a C=O group are obtained. Obviously, these products are formed via sulfur-exchange reactions.

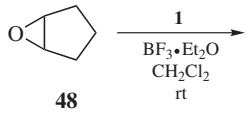


45

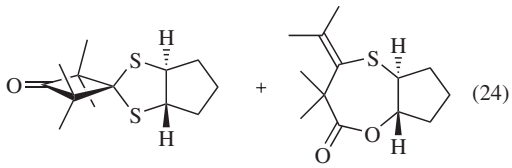
(23)

46 **47**

In the case of cyclopentene oxide (**48**), only secondary products **49** and **50**, which are formed in multistep reactions, are obtained in low yields (eq 24).



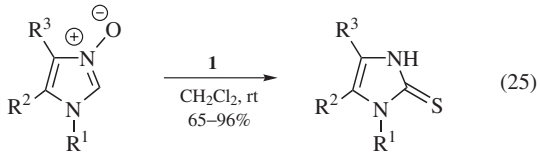
48



(24)

49 **50**

An efficient synthesis of imidazole-2-thiones (**52**) from 2-unsubstituted imidazole-3-oxides (**51**) and 0.5 equiv of **1** is described (eq 25).[40] The smooth sulfur-transfer occurs via an intermediate [2+3]-cycloadduct analogous to the products observed in reactions with nitrones (eq 16).

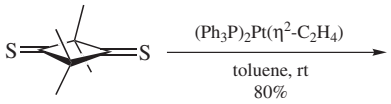


(25)

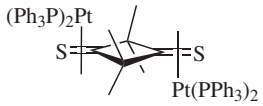
51 **52**

The photolysis ($\lambda > 400$ nm) of **1** in 2-propanol in the presence of oxygen and in the absence of a sensitizer gives 2,2,4,4-tetramethylcyclobutane-1,3-dione.[2] In toluene solution, **1** and 2

equiv of $(Ph_3P)_2Pt(\eta^2\text{-}C_2H_4)$ combine to give the bis-(platinum) complex **53** (eq 26).[41]



1



53 (26)

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